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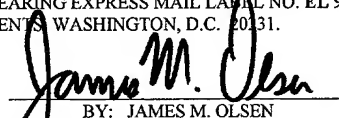
International Application No. PCT/DE00/01485

PATENT  
Attorney Docket No. AC FZK 4903 (JT-8)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

CERTIFICATE OF EXPRESS MAIL  
(37 C.F.R. § 1.10)

I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE, EXPRESS MAIL POST OFFICE TO ADDRESSEE<sup>®</sup> UNDER 37 C.F.R. § 1.10, BEARING EXPRESS MAIL LABEL NO. EL 928737387 US ON THIS 13th DAY OF NOVEMBER, 2001 AND IS ADDRESSED TO: COMMISSIONER FOR PATENTS WASHINGTON, D.C. 20531.

  
BY: JAMES M. OLSEN

INT'L APPL. NO.: PCT/DE00/01485	)	
	)	
INT'L FILING DATE: May 11, 2000	)	
	)	
APPLICANT: Valeri KISELEV et al.	)	Art Unit: Unassigned
	)	
SERIAL NO.: To be assigned	)	Examiner: Unassigned
	)	
FILED: November 12, 2001	)	
	)	
FOR: COMPUTER FOR ANALYZING	)	
DATA FROM MEASUREMENTS	)	
OF NUCLEAR MAGNETIC	)	
RESONANCE, NUCLEAR	)	
TOMOGRAPH PROVIDED WITH	)	
SAID COMPUTER, AND METHOD	)	
FOR ANALYZING DATA FROM	)	
MEASUREMENTS OF NUCLEAR	)	
MAGNETIC RESONANCE	)	

Commissioner for Patents  
Box PCT  
Washington, D.C. 20231

**TRANSMITTAL OF APPLICATION PAPERS TO U.S.  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. § 371 (37 CFR 1.494 OR 1.495)**

This transmittal letter is based upon Form PTO-1390 (as revised in May, 1993).

**International Application No. PCT/DE00/01485**

The above-identified applicant(s) have filed an International Application under the PCT and hereby submit(s) to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is the FIRST submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is the SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. §371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay.
4. ☒ A proper Demand for International Preliminary Examination (IPE) was made to the appropriate Authority (IPEA) by the 19th month from the earliest claimed priority date (see attached).
5. ☒ A copy of the International Application as amended (35 U.S.C. §371(c)(2)) -
  - (a) ☒ is transmitted herewith (required when not transmitted by International Bureau). See WIPO Publication WO 00/72035.
  - (b) ☐ has been transmitted by the International Bureau.
  - (c) ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into the English language is enclosed.  
As well as two (2) sheets of drawings.
7. ☒ Amendments to the (specification and) claims of the International Application under PCT Article 19 (35 U.S.C. §371 (c)(3))
  - (a) ☐ are transmitted herewith (required if not transmitted by the International Bureau).
  - (b) ☐ have been transmitted by the International Bureau.
  - (c) ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - (d) ☒ have not been made and will not be made.
  - (e) ☐ will be submitted with the appropriate surcharge.
8. ☐ A translation of the amendments to the claims (and/or the specification) under PCT Article 19 (35 U.S.C. §173(c)(3)) is enclosed or will be submitted with the appropriate surcharge.
9. ☒ An unexecuted Oath or Declaration/Power of Attorney of the inventor(s) (35 U.S.C. §371(c)(4)) is enclosed.

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10. ☐ A translation of at least the Annexes to the IPE Report under PCT Article 36 (35 U.S.C. §371(c)(5)) is enclosed.

**Items 11. to 16. below concern other document(s) or information included:**

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98 is enclosed.
12. ☐ An Assignment is enclosed for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31. is included.
13. ☒ A FIRST preliminary amendment is enclosed. **IT IS REQUESTED THAT THE FILING FEES FOR THE CLAIMS BE CALCULATED AFTER THE CLAIM AMENDMENTS IN THE PRELIMINARY AMENDMENT HAVE BEEN ENTERED.**
14. ☐ A substitute specification (including claims, abstract, drawing) is enclosed.
15. ☐ A change of Power of Attorney and/or address letter is enclosed.
16. ☒ Other items of information:
- ☒ This application is being filed pursuant to 37 CFR 1.494(c) or 1.495(c), and any **missing parts** will be filed before expiration of -
- ☐ 22 months from the priority date under 37 CFR 1.494(c), or
- ☒ 32 months from the priority date under 37 CFR 1.495(c).
- ☒ The undersigned attorney is authorized by the International application and by the inventors to enter the **National Phase** pursuant to 37 CFR 1.494(c) or 1.495(c).

The following additional information relates to the International Application:

- ☒ Receiving Office: Germany
- ☒ IPEA (if filing under 37 CFR 1.495): EPO
- ☒ Priority claim(s) (35 USC §§ 119, 365): German App. No. 199 23 587.2, Filed: May 22, 1999
- ☒ A copy of the International Search Report is
- ☐ will follow
- ☒ attached to the copy of the International Application.

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International Application No. PCT/DE00/01485

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☒ A copy of the Receiving Office Request Form is enclosed.

17. ☐ Form PTO/SB/05 (1) sheet

18. ☐ Small Entity Form

The fee calculation is set forth below.

FEE CALCULATION

☒ A check in payment of the filing fee, calculated as follows, is attached (37 CFR 1.492)

Basic Fee \$890.00

Total Number of claims  
in excess of (20) times \$18 x (1) = \$18.00

Number of independent claims  
in excess of (3) times \$80 \$0.00

Fee for multiple dependent  
claims \$270 \$0.00

TOTAL FILING FEE \$908.00

Kindly send us the official filing receipt.

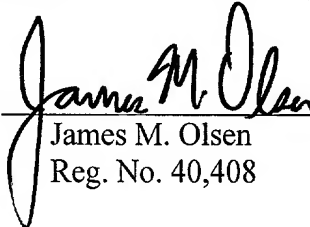
The Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 03-2775. This is a "general authorization" under 37 CFR 1.25(b), except that no automatic debit of the issue upon allowance is authorized.

Respectfully submitted,

CONNOLLY BOVE LODGE & HUTZ LLP

Date: November 13, 2001

By:

  
James M. Olsen  
Reg. No. 40,408

10/019370

531 Rec'd PCT/

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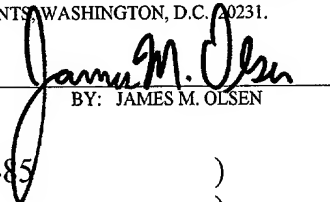
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MEASUREMENTS OF NUCLEAR )  
MAGNETIC RESONANCE )

Commissioner for Patents  
Box PCT  
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to the examination of the above application, please amend this application as follows:

**IN THE CLAIMS:**

Please amend claims 3, 8, 9, 11, 14, 17, and 19, as follows:

3. A nuclear magnetic resonance tomograph characterized in that it comprises at least one computer according to Claim 1.

8. The method according to Claim 4, characterized in that the relaxation signal is divided into at least one part that is dependent on the echo time  $T_E$  and into at least one part that is not dependent on the echo time  $T_E$ .

9. The method according to Claim 4, characterized in that at least one signal is determined that is proportional to  $T_E \exp(-T_E / T_2')$ .

11. The method according to Claim 4, characterized in that statistical fluctuations of  $\Delta T_2'$  are ascertained.

14. The method according to Claim 4, characterized in that a statistical deviation of an initial intensity  $S_0$  is ascertained.

17. The method according to Claim 4, characterized in that a statistical fluctuation of a noise signal  $g$  is ascertained.

19. The method according to Claim 4, characterized in that the recorded data is

acquired in an at least two-dimensional field, whereby a field axis (DTE) acquires echo times  $T_E$  and whereby another field axis (DTR) reproduces repetitions of excitations at a time interval  $T_R$ .

**Amendments to the claims are set forth in bracket and underline format in Exhibit A, attached herewith.**

### REMARKS

Applicants have amended the above-mentioned claims in order to place them in proper U.S. claim format and eliminate multiple dependencies. Thus, the claim amendments relate to form and should in no way be construed as being for any reason related to the patentability of these claims.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 03-2775.

Respectfully submitted,

CONNOLLY BOVE LODGE & HUTZ LLP

Dated: November 13, 2001

By: 

James M. Olsen  
Reg. No. 40,408

## EXHIBIT A – AMENDMENTS TO CLAIMS

### IN THE CLAIMS:

Please amend claims 3, 8, 9, 11, 14, 17, and 19, as follows:

3. (Amended) A nuclear magnetic resonance tomograph characterized in that it comprises at least one computer according to [one of Claims] Claim 1 [or 2].

8. (Amended) The method according to [one of Claims] Claim 4<sub>2</sub> [through 7,] characterized in that the relaxation signal is divided into at least one part that is dependent on the echo time  $T_E$  and into at least one part that is not dependent on the echo time  $T_E$ .

9. (Amended) The method according to [one of Claims] Claim 4<sub>2</sub> [through 8,] characterized in that at least one signal is determined that is proportional to  $T_E \exp(-T_E / T_2^*)$ .

11. (Amended) The method according to [one or more of Claims] Claim 4<sub>2</sub> [through 10,] characterized in that statistical fluctuations of  $\Delta T_2^*$  are ascertained.

14. (Amended) The method according to [one of Claims] Claim 4<sub>2</sub> [through 13,] characterized in that a statistical deviation of an initial intensity  $S_0$  is ascertained.

17. (Amended) The method according to [one of Claims] Claim 4<sub>2</sub> [through 16,] characterized in that a statistical fluctuation of a noise signal  $g$  is ascertained.

19. (Amended) The method according to [one of Claims] Claim 4<sub>2</sub> [through 18,]



characterized in that the recorded data is acquired in an at least two-dimensional field, whereby a  
field axis (DTE) acquires echo times  $T_E$  and whereby another field axis (DTR) reproduces  
repetitions of excitations at a time interval  $T_R$ .

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**TRANSLATION**

PT 0.1866

May 22, 1999

***Description***

Computer for analyzing data from measurements of nuclear magnetic resonance,  
nuclear magnetic resonance tomograph provided with said computer,  
and method for analyzing data from measurements of nuclear magnetic resonance

The invention pertains to a computer for analyzing data from measurements of nuclear magnetic resonance, whereby the data contains at least one relaxation signal of a sample.

The invention also relates to a nuclear magnetic resonance tomograph and to a method for analyzing data from measurements of nuclear magnetic resonance, a process in which at least one relaxation signal of a sample is determined.

Nuclear magnetic resonance (NMR) is employed in order to obtain a contrast image of an object or spectroscopic information about a substance. Magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) make it possible to examine regional hemodynamics *in vivo* with changes in blood volumes and blood states as well as changes in the metabolism as a function of brain activity; see: S. Posse *et al.*: Functional Magnetic Resonance Studies of Brain Activation; Seminars in Clinical Neuropsychiatry, Vol. 1, No. 1, 1996, pages 76 through 88.

Particularly in medical research, there is a need to acquire information about brain activity by means of measurements of blood flow or changes in the concentration of deoxyhemoglobin. Neuronal activation is manifested by an increase of the blood flow into activated regions of the brain, whereby a drop occurs in the concentration of deoxyhemoglobin. Deoxyhemoglobin (DOH) is a paramagnetic substance that reduces the magnetic field homogeneity and thus accelerates the signal relaxation. If the DOH concentration drops due to brain activity that triggers blood flow, then the signal relaxation in the active regions of the brain is modulated. It is primarily the protons of hydrogen in water that are excited. A localization of brain activity is made possible by conducting an examination with functional NMR methods that measure the NMR signal with a time delay (echo time). This is also referred to as a susceptibility-sensitive measurement. The biological mechanism of action is known in the literature under the name

BOLD effect (Blood Oxygenation Level Dependence effect) and, in susceptibility-sensitive magnetic resonance measurements at a field strength of a static magnetic field of, for example, 1.5 tesla, it leads to fluctuations of the image brightness of up to 10% in activated regions of the brain. Instead of the endogenous contrast agent DOH, other contrast agents can also occur that cause a change in the susceptibility. NMR imaging methods select slices or volumes that yield a measurement signal under appropriate irradiation with high-frequency pulses and under the application of magnetic gradient fields; this measurement signal is digitized and stored in a two-dimensional or three-dimensional field in the measuring computer.

A two-dimensional or three-dimensional Fourier transform on the basis of the raw data collected then serves to acquire (reconstruct) the desired image information.

A reconstructed slice image consists of pixels (picture elements), and a volume data set consists of voxels (volume elements). A pixel is a two-dimensional picture element, for instance, a square. The image is made up of the pixels. A voxel is a three-dimensional volume element, for example, a cube which, for metrological reasons, does not exhibit any sharp boundaries. The dimensions of a pixel normally lie in the order of magnitude of  $1 \text{ mm}^2$ , and those of a voxel in the order of magnitude of  $1 \text{ mm}^3$ . The geometries and dimensions can vary.

Since experiments have shown that it is never possible to assume a strictly two-dimensional plane in the case of slice images, the term voxel is often employed here as well since this takes into consideration the fact that the image planes extend into the third dimension.

By comparing the measured signal course in every pixel with the time course of a model function, a stimulus-specific neuronal activation can be detected and spatially localized. A stimulus can be, for instance, a somatosensorial, acoustic, visual or olfactory stimulus as well as a mental or motor task. The model function or the model time series describes the anticipated signal change of the magnetic resonance signal resulting from neuronal activation. These can be derived, for example, by means of empirical rules from a paradigm of the experiment in question. The essential aspect is to take into consideration a time delay of the model function with respect to the paradigm (sluggish reaction of the blood flow in response to neuronal activation).

It is already known how brain activation can be depicted by activation images acquired from nuclear spin tomographic data. The activation images can even be com-

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puted and displayed in real time, that is to say, a data set can be converted into an image before the next data set is measured. Here, the time interval is typically 1 to 3 seconds.

Such a computation and reproduction of the activation images in real time are described in US patent no. 5,657,758. This method is characterized by the fact that it allows a high resolution, both in terms of time and space.

Another known method is presented in the articles by Jezzard, P. *et al.*, Proc. SMRM 1993, page 1392; Biswal, B. *et al.*, MRM 34 (1995) page 537 and Purdon, P. *et al.*, Proc. ISMRM 1998, page 253. This method makes use of a measuring signal and a paradigm of the measurement. Both signals undergo a Fourier transform.

The known methods analyze the similarity between the signal of the paradigm and of the measured data.

The invention has the objective of carrying out a method of the known type in such a way that the highest possible contrast-to-noise ratio is achieved.

According to the invention, this objective is achieved in that a computer of the known type is configured in such a way that the computer operates with at least one analyzing means, whereby said analyzing means separates the data into at least two parts that are differently dependent on an echo time  $T_E$ .

In particular, the invention provides for a computer with which a fast spectroscopic imaging method can be realized that detects the changes in the NMR signal relaxation using a time constant  $T_2^* = \frac{1}{R_2^*}$  at several points in time following excitation.

This spectroscopic imaging method is preferably an echo-planar imaging method, especially a repeated two-dimensional echo-imaging method consisting of a repeated use of two-dimensional echo-planar image encoding. Spatial encoding takes place within the shortest possible time span that is repeated several times during one signal decay and preferably ranges from 20 ms to 100 ms. The multiple repetition of the echo-planar encoding during one signal decay depicts the course of the signal decay in the sequence of reconstructed individual images.

A practical conventional echo-planar method is designated as EPI (Echo-Planar-Imaging). An advantageous implementation of the method according to the invention is done by means of TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging).

The number of images that are encoded during the signal decay is dependent on the relaxation time and on the encoding time  $\Delta t$  for a single image.

Preferably, a computer is used to analyze data from nuclear magnetic resonance tomography, a process in which the data contains at least one relaxation signal of a sample and in which the data is separated into parts that are dependent on an echo time  $T_E$  and into at least one more component that is not dependent on the echo time  $T_E$  and whereby the signals that are dependent on an echo time  $T_E$  are acquired as activation signals.

A noise signal can be detected in that the computer operates with at least one analyzing means which separates the data into at least one part that is dependent on an echo time  $T_E$  and into another component that is not dependent on the echo time  $T_E$ , whereby the analyzing means acquires signals that are dependent on an echo time  $T_E$  as activation signals.

A separation of several components of a function to be examined can be ascertained by determining the signals that have a different dependence on the echo time  $T_E$ . Thus, it is possible, for instance, to separate an amplitude  $s_0$  from a time constant  $T_2^*$  and/or from a noise signal  $g$ .

Moreover, the invention relates to a nuclear magnetic resonance tomograph that comprises at least one computer according to the invention.

The invention also provides that a method to analyze data from nuclear magnetic resonance tomography -- whereby at least one relaxation signal of a sample is determined -- is carried out in such a way that the data is separated into at least two parts having a different dependence on an echo time  $T_E$ .

Preferably, the process is to be carried out in such a way that intensity values of the measured data for identical echo times are acquired in at least two different recordings of the relaxation signal and in that a dependence of the intensity values on the echo time  $T_E$  is subsequently acquired and in that the relaxation signal is separated into parts having a different dependence on the echo time  $T_E$ .

Preferably, the method should be carried out in such a way that the relaxation signal is divided into a part that is dependent on an echo time  $T_E$  and into at least one part that is not dependent on the echo time  $T_E$  and so that the part that is dependent on the echo time  $T_E$  is acquired as an activation signal.

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In this context, it is especially advantageous for at least one signal to be detected that is proportional to  $T_E \exp(-T_E / T_2^*)$ , whereby the value of  $T_2^*$  is determined particularly by means of a preferably separate fit procedure on the basis of the same data.

Here, it is particularly practical for  $T_2^*$  to be calculated with the following formula:

$$S = S_0 \exp(-T_E / T_2^*) + g.$$

Furthermore, it is advantageous to carry out the method in such a way that the statistical fluctuations of  $\Delta T_2^*$  are determined.

In this context, it is especially practical for a standard deviation  $\sigma(\Delta T_2^*)$  to be calculated.

It is likewise advantageous for a quotient  $\sigma(\Delta T_2^*) / T_2^*$  to be formed and acquired as a measure of an activity.

Here, it is particularly practical for a statistical deviation of an initial intensity  $S_0$  to be determined.

Here, it is advantageous for a standard deviation  $\sigma(S_0)$  to be calculated.

In this context, it is preferable for a quotient  $\sigma(S_0) / S_0$  to be calculated.

Particular preference is given to carrying out the method in such a way that a statistical fluctuation of a noise signal  $g$  is determined.

Here, it is especially advantageous for a standard deviation  $\sigma(g)$  of  $g$  to be formed.

Moreover, the method is preferably carried out in such a way that the recorded data is acquired in an at least two-dimensional field, whereby a field axis (DTE) acquires echo times  $T_E$  and whereby another field axis (DTR) reproduces repetitions of excitations at a time interval  $T_R$ .

Here, it is particularly advantageous for  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  to be determined by means of the following steps:

- (i) adaptation of signals averaged over the other field axis (DTR) to an exponential decay as a function of the first field axis (DTE) and determination of  $S_0$  and  $T_2^*$ ;
- (ii) calculation of  $\sigma(\Delta S_0)$ ,  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  for several voxels and different  $T_E$ , followed by averaging of these values over at least one region of interest (ROI);
- (iii) adaptation of

$$\frac{\sigma(\Delta S)}{S_0} = \left\{ \left[ \left( \frac{T_E}{T_2^*} \right)^2 \left( \frac{\sigma(\Delta T_2^*)}{T_2^*} \right)^2 + \left( \frac{\sigma(\Delta S_0)}{S_0} \right)^2 - 2 \frac{T_E}{T_2^*} \frac{\langle \Delta S_0 \Delta T_2^* \rangle}{S_0 T_2^*} \right] e^{-2T_E/T_2^*} + \left( \frac{\sigma(g)}{S_0} \right)^2 \right\}^{1/2}$$

and determination of  $\sigma(\Delta S) / S_0$  as a function of  $T_E$ .

Here, it is particularly advantageous for the expression  $\langle \Delta S_0 \Delta T_2^* \rangle = 0$  to be used for the adaptation of  $\sigma(\Delta S) / S_0$ .

Additional advantages, special features and practical refinements of the invention can be gleaned from the subordinate claims and from the following presentation of preferred embodiments of the invention with reference to model calculations, drawings and a table.

The drawings show the following:

- Figure 1 - multi-echo sequence with several measuring sequences, each of which follows a spin excitation (\*) and involving the acquisition of various echo times  $T_E$ ;
- Figure 2 - a schematic diagram that serves to illustrate a method involving the separate preparation of data for each of the echo times;
- Figure 3 - an experimental differential signal of a functional relaxation time change in a selected picture element as a function of the measuring time following a signal excitation;
- Figure 4 -  $\Delta S$  from various voxels averaged over a few ROIs as a function of  $T_E$  for two representative persons;
- Figure 5 - in the upper portion of the image, a detection of brain activation in four steps by means of a conventional imaging method and, in the lower portion of the image, a detection of brain activation by means of a method according to the invention.

The table shows a compilation of the experimental sample data.

Figure 1 depicts a multi-echo sequence with several measuring sequences, each of which follows a spin excitation (\*) and involving the acquisition of various echo times  $T_E$ .

The measuring sequences of the multi-echo sequence were determined by means of the Turbo-PEPSI method. Each of the measuring sequences contains twelve echo sig-

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nals with echo times that lie between 12 and 213 ms. The echo times were each acquired in the form of a time interval  $\Delta T_E$  lasting 18.3 ms.

The values given for the echo times and the time intervals are each adapted to the speed of the data processing. Particularly in the case of a further improvement in scanner technology, it will be possible to raise the number of echo signals and to shorten the time intervals  $\Delta T_E$ .

Figure 2 depicts a schematic diagram showing how differing measuring sequences are used to acquire a signal at a first echo time or at a second or subsequent echo time.

In the curve depicted in Figure 3, a measuring signal  $\sigma(S)$  has been acquired as a function of the echo time. It shows a principle involving a fit procedure that serves to divide the measuring signal  $\sigma(S)$  into components that are dependent on  $T_2^*$  and into noise that is not dependent on  $T_E$ . The measuring signal  $\sigma(S)$  consists of a part that is dependent on an amplitude  $S_0$  and of a part that is dependent on a relaxation time  $T_2^*$  and of a constant noise signal  $g$ .

In particular, the invention provides for achieving a differentiation between activation signals and noise by means of an analysis of the course of time of the measured data and/or their statistical distribution.

The analysis method according to the invention can be checked experimentally, for example, by means of nuclear spin tomographic examinations of the brains of test subjects. A source of light, especially a matrix of light-emitting diodes (LED), is positioned directly in front of the face of the test subjects and then excited so as to emit flash signals. The frequency of excitation is 8 Hz. The effect of the signal flashes is exerted over a time interval - synchronized with the carrier signal from a scanner - of several seconds, for instance, 5 seconds, which is followed by a rest interval of approximately the same duration. The scanner is a Vision 1.5 Tesla, full-body scanner made by Siemens Medical Systems of Erlangen, Germany, with a magnetic field gradient of 25 mT/m. Such a scanner is able to switch over gradient fields within about 600  $\mu$ s.

TURBO-PEPSI (Proton Echo Planar Spectroscopic Imaging) was employed as the spectroscopic imaging method.

Data adaptation was performed according to the exponential function:

$$S = S_0 e^{-T_E/T_2^*}$$

making use of a non-linear least-square-fit.



A differentiation between activation and noise by means of multi-echo fMRI will be presented below.

The detection of physiological noise (caused, for example, by heart beat) calls for a stationary frequency spectrum, for adequate temporal resolution as well as for prior knowledge about the spatial and temporal characteristics of the noise. According to the invention, a new method for differentiating between BOLD-related variations and other fluctuations of the MR signal (caused, for instance, by thermal noise) is being proposed that can completely do without any prior knowledge of a stimulation paradigm. This method is based on a single-shot-multi-echo sequence like the Turbo-PEPSI technique described in the article by Posse, S. *et al.* in PROC. ISMRM 1998, page 299. Reference is hereby made to the entire text of this publication.

Following signal excitation, its relaxation behavior is recorded at equidistant time intervals  $T_E$ . This is repeated several times at time intervals of  $T_R$  seconds. In such an experiment, the signal of each voxel forms a two-dimensional field with the echo times  $T_E$  in one direction (DTE) and with the repetitions at the time interval  $T_R$  in the other direction (DTR). The relaxation is assumed to be monoexponential,  $S = S_0 \exp(-T_E / T_2^*) + g$ , with a hardware-dependent noise  $g$  that we can consider as white in both domains, DTE and DTR. The values  $S_0$  and  $T_2^*$  are constant in DTE but they vary in DTR:  $S_0$ , for instance, due to hardware instabilities or blood flow effects and  $T_R$ , for instance, due to the test subject stimulation. Variations in  $T_2^*$  indicate changes in the local blood flow. In the case of relatively small changes  $\Delta S_0$  and  $\Delta T_2^*$ , the signal changes can be formulated as follows:

$$\frac{\Delta S}{S_0} = \left\{ \left[ \left( \frac{T_E}{T_2^*} \right)^2 \left( \frac{\sigma(\Delta T_2^*)}{T_2^*} \right)^2 + \left( \frac{\sigma(\Delta S_0)}{S_0} \right)^2 - 2 \frac{T_E}{T_2^*} \frac{\langle \Delta S_0 \Delta T_2^* \rangle}{S_0 T_2^*} \right] e^{-2 T_E / T_2^*} + \left( \frac{\sigma(g)}{S_0} \right)^2 \right\}^{1/2} \quad [1]$$

wherein  $\langle A \rangle$  and  $\sigma(A)$  correspond to the mean value and to the standard deviation of a quantity  $A$  in DTR. Further analysis depends on the actual magnitude of the terms used in [1]. It is practical, under experimental conditions, for  $\Delta S_0$  to be negligible both in the resting and in the activation phases (except in the sagittal sinus). The quantities  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  are determined as follows: (i) adaptation of the signal averaged over the DTR to the monoexponential decay as a function of DTE in order to determine  $S_0$  and  $T_2^*$ ; (ii) calculation of  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  for each voxel and for each  $T_E$  and averaging of those values over the region of interest (ROI); (iii) adaptation of [1] with  $\Delta S_0 = 0$  to these val-

ues as a function of  $T_E$ . This is possible because local brain activation is manifested by an increase of  $T_2^*$ , which displays a characteristic  $T_E$ -dependence proportional to  $T_E e^{-T_E/T_2^*}$ , in contrast to which the value of the white noise does not depend on  $T_E$  (see figures). The  $T_E$ -dependence of the signal outside of the brain is approximated by a constant. In order to validate this method, the quantity of white noise is compared to the noise outside of the brain, taking into consideration that  $\sigma$  (g) is reduced outside of the brain. For a Gaussian distribution, this reduction factor is 0.6028.

Visual stimulation experiments involving four healthy test subjects were carried out employing a Siemens Vision-1.5-Tesla scanner. By means of a multi-layer Turbo-PEPSI sequence, 12 EPI images (matrix size:  $64 \times 32$  pixels; pixel size:  $3 \times 6$  mm<sup>2</sup>) were acquired of a single FID, 90° flip angle at echo times ranging from 12 to 228 ms. A conventional correlation analysis was carried out with the Stimulate software package, with the use of a boxcar reference vector.

Figure 4 shows  $\Delta S$  from various voxels averaged over a few ROIs as a function of  $T_E$  for two representative persons. The variability of all values over ROIs was small (10% to 20%). The ROIs were located in the visual cortex (vc), in the motor cortex (mc), in the white matter (wm) and outside of the brain, circumventing areas outside of the brain that are characterized as phantom images (out). The filter results from [1] are compiled in the table; wherever the abbreviated ROI designations are followed by the number of voxels between parentheses, the mean correlation coefficient is normalized over a ROI,  $\sigma$  (g) of the ROI outside of the brain, to the mean  $S_0$  of the inner ROIs and the errors in all values are defined as a standard deviation.

**Table 1**

ROI	$\Delta S$	$(\Delta S / \sigma(g))$	$(\Delta S / S_0)$
vc (20)	$0.62 \pm 0.21$	$4.3 \pm 0.1$	$0.75 \pm 0.05$
mc (20)	$-0.11 \pm 0.14$	$0.26 \pm 0.16$	$0.79 \pm 0.05$
wm (21)	$-0.009 \pm 0.19$	$-0.001 \pm 5$	$0.93 \pm 0.07$
out (21)	$-0.19 \pm 0.11$	not fitted	$0.66 \pm 0.01$
vc (28)	$0.67 \pm 0.12$	$3.6 \pm 0.1$	$0.42 \pm 0.07$
mc (32)	$-0.22 \pm 0.14$	$-0.6 \pm 0.8$	$0.72 \pm 0.06$
wm (32)	$-0.29 \pm 0.06$	$-0.4 \pm 1.2$	$0.64 \pm 0.06$
out (38)	$-0.12 \pm 0.25$	not fitted	$0.45 \pm 0.01$



qualitative relaxation time change. This allows the use of imaging having the highest possible bandwidth (shortest encoding time) for the smallest spatial distortion possible and also to achieve maximum measuring sensitivity by measuring an optimal number of encodings following signal excitation.

The analysis method can be used in real time measurements in order to directly analyze the relaxation changes.

In addition, the analysis methods according to the invention are particularly versatile. It has been proven to be practical to employ a summation or, even more advantageously, a weighted summation which, in comparison to a curve adaptation, can be done faster and without any loss of the measuring sensitivity. A summation, or a weighted summation, has the advantage that it constitutes a particularly reliable analysis method.

All of the test subjects exhibited a strong activation in the primary visual cortex ( $V_1$ ) and in the neighboring regions. The changes observed in the functional signal measured with TURBO-PEPSI amount to up to 10%, depending on the relaxation time  $T_2^*$ , the position and the test subject in question.

The excitation exhibits a maximum in the vicinity of  $T_E = T_2^*$ . A comparison of EPI and TURBO-PEPSI images with  $T_E = 72.5$  ms revealed very similar activation images.

The gain in sensitivity is particularly advantageous for real time measurements since a change in the relaxation can be effectively ascertained, even with just a few measured values. In summary, it can be said that the multi-echo detection of the differential signal translates into optimal sensitivity for various magnetic field strengths.

Furthermore, the invention can be utilized in echo-planar imaging (EPI), in phase-encoded imaging methods as well as in spectroscopic imaging methods.

The examples presented serve to elucidate the computer and the analysis method on the basis of NMR measurements on the human brain. Naturally, the computer, the nuclear resonance tomograph as well as the analysis method can also be used to examine other samples of either living or non-living material.

**Patent Claims**

1. A computer for analyzing data from nuclear magnetic resonance, whereby the data contains at least one relaxation signal of a sample, characterized in that the computer operates with at least one analyzing means that separates the data into at least two parts that are differently dependent on an echo time  $T_E$ .
2. The computer according to Claim 1, characterized in that the analyzing means separates the data into at least one part that is dependent on an echo time  $T_E$  and into at least one more component that is not dependent on the echo time  $T_E$  and whereby the analyzing means acquires the signals that are dependent on an echo time  $T_E$  as activation signals.
3. A nuclear magnetic resonance tomograph characterized in that it comprises at least one computer according to one of Claims 1 or 2.
4. A method to analyze data from nuclear magnetic resonance, whereby at least one relaxation signal of a sample is detected, characterized in that the data is separated into at least two parts having a different dependence on an echo time  $T_E$ .
5. The method according to Claim 4, characterized in that the intensity values of the measured data are acquired and separated into at least two different dependencies on the echo time  $T_E$ .
6. The method according to Claim 5, characterized in that a measure of a statistical variation of the intensities is determined.
7. The method according to Claim 6, characterized in that a standard deviation of the intensities is ascertained.

8. The method according to one of Claims 4 through 7, characterized in that the relaxation signal is divided into at least one part that is dependent on the echo time  $T_E$  and into at least one part that is not dependent on the echo time  $T_E$ .
9. The method according to one of Claims 4 through 8, characterized in that at least one signal is determined that is proportional to  $T_E \exp(-T_E / T_2^*)$ .
10. The method according to Claim 9, characterized in that  $T_2^*$  is ascertained with the formula  $S = S_0 \exp(-T_E / T_2^*) + g$ .
11. The method according to one or more of Claims 4 through 10, characterized in that statistical fluctuations of  $\Delta T_2^*$  are ascertained.
12. The method according to Claim 11, characterized in that a standard deviation  $\sigma(\Delta T_2^*)$  is ascertained.
13. The method according to Claim 12, characterized in that a quotient  $\sigma(\Delta T_2^*) / T_2^*$  is formed and acquired as a measure of an activity.
14. The method according to one of Claims 4 through 13, characterized in that a statistical deviation of an initial intensity  $S_0$  is ascertained.
15. The method according to Claim 14, characterized in that a standard deviation  $\sigma(\Delta S_0)$  is ascertained.
16. The method according to Claim 15, characterized in that a quotient  $\sigma(\Delta S_0) / \Delta S_0$  is ascertained.

17. The method according to one of Claims 4 through 16, characterized in that a statistical fluctuation of a noise signal  $g$  is ascertained.
18. The method according to Claim 17, characterized in that a standard deviation  $\sigma(g)$  of  $g$  is formed.
19. The method according to one of Claims 4 through 18, characterized in that the recorded data is acquired in an at least two-dimensional field, whereby a field axis (DTE) acquires echo times  $T_E$  and whereby another field axis (DTR) reproduces repetitions of excitations at a time interval  $T_R$ .
20. The method according to Claim 19, characterized in that  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  are determined by means of the following steps:
- adaptation of signals averaged over DTR to an exponential decay as a function of DTE and determination of  $S_0$  and  $T_2^*$ ;
  - calculation of  $\sigma(\Delta S_0)$ ,  $\sigma(\Delta T_2^*)$  and  $\sigma(g)$  for several voxels and different  $T_E$ , followed by averaging of these values over at least one region of interest (ROI);
  - adaptation of

$$\frac{\sigma(\Delta S)}{S_0} = \left\{ \left[ \left( \frac{T_E}{T_2^*} \right)^2 \left( \frac{\sigma(\Delta T_2^*)}{T_2^*} \right)^2 + \left( \frac{\sigma(\Delta S_0)}{S_0} \right)^2 - 2 \frac{T_E}{T_2^*} \frac{\langle \Delta S_0 \Delta T_2^* \rangle}{S_0 T_2^*} \right] e^{-2 T_E / T_2^*} + \left( \frac{\sigma(g)}{S_0} \right)^2 \right\}^{1/2}$$

and determination of  $\sigma(\Delta S) / S_0$  as a function of  $T_E$ .

21. The method according to Claim 20, characterized in that the expression  $\langle \Delta S_0 \Delta T_2^* \rangle = 0$  is used for the adaptation of  $\sigma(\Delta S_0) / S_0$ .

**Abstract**

The invention pertains to a computer for analyzing data from nuclear magnetic resonance tomography, whereby the data contains at least one relaxation signal of a sample.

According to the invention, the computer is designed in such a way that the computer operates with at least one analyzing means that separates the data into at least two parts that are differently dependent on an echo time  $T_E$ .

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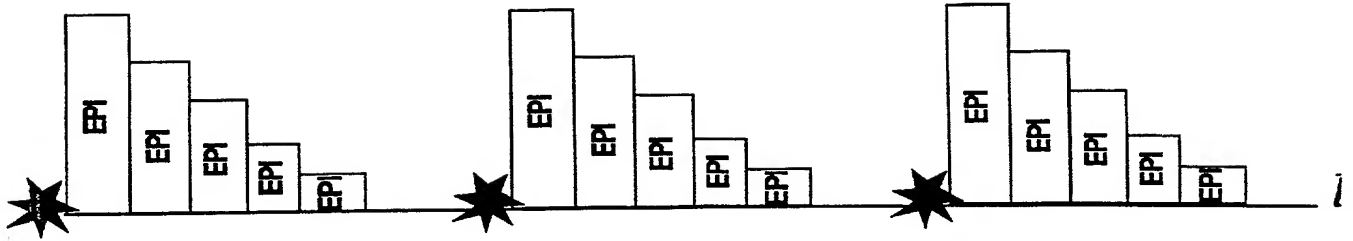


Fig. 1

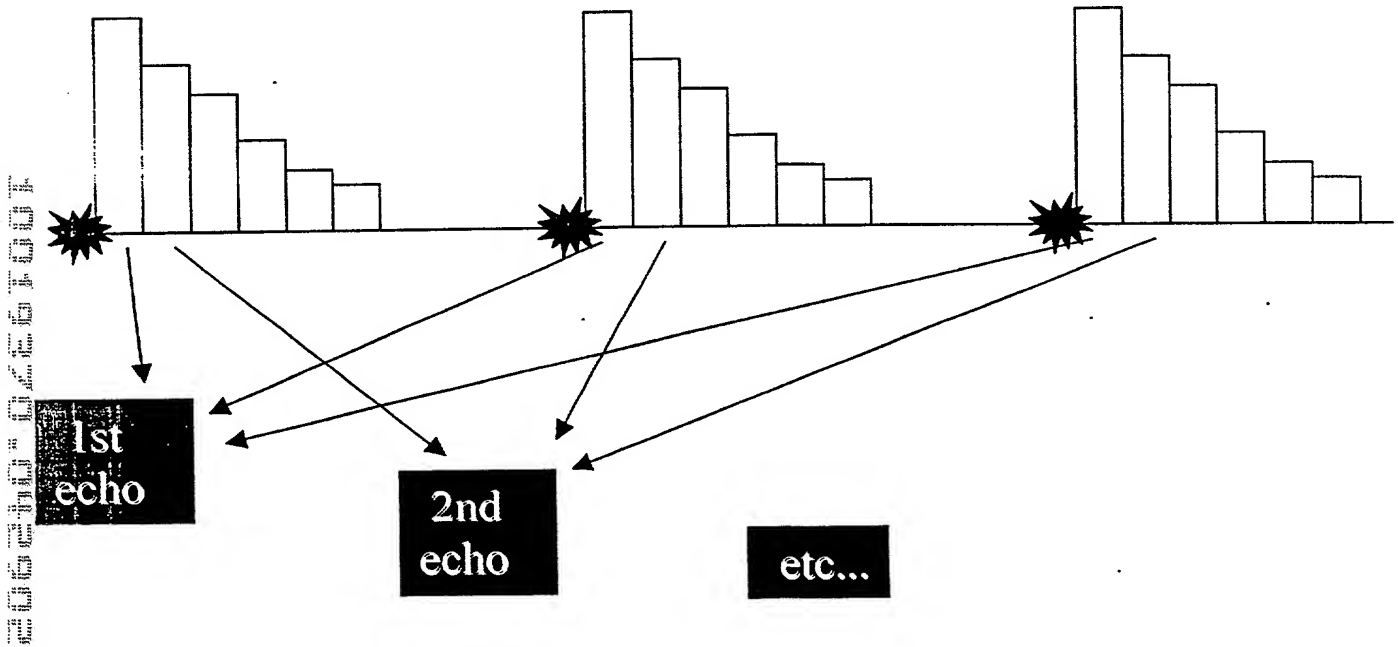


Fig. 2

$$\sigma(s) = \text{TE} + \text{[exponential decay]} + \text{[bell curve]} + \text{[step function]}$$

Fig. 3

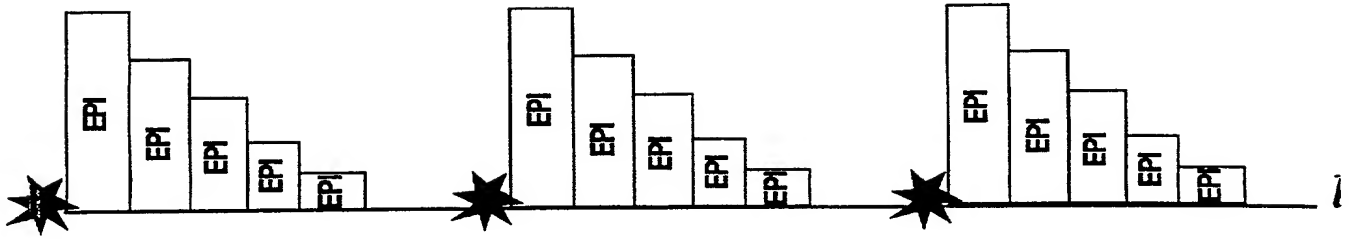


Fig. 1

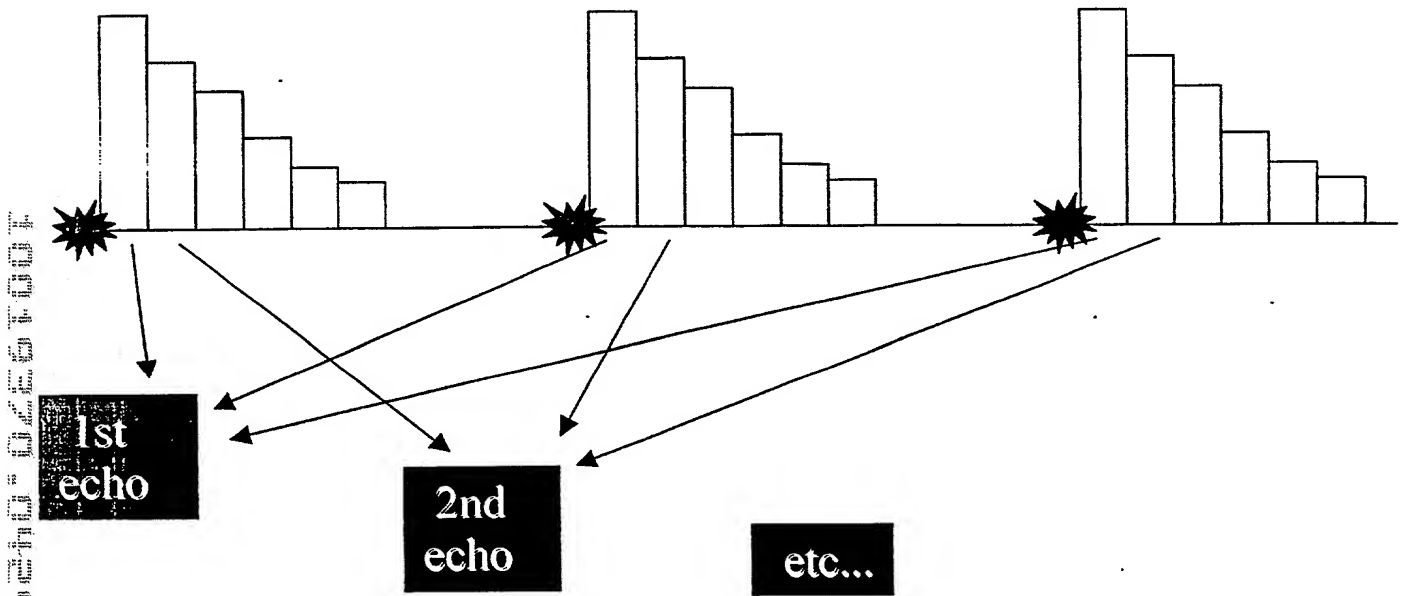


Fig. 2

$$\sigma(s)_{TE} = \text{[Graph 1]} + \text{[Graph 2]} + \text{[Graph 3]}$$

The equation shows the decomposition of a function  $\sigma(s)$  at TE into three components. The first component is a bell-shaped curve. The second component is a graph with a linearly decreasing line from a positive value on the y-axis to zero. The third component is a graph with a bell-shaped curve starting from the origin and decaying to zero.

Fig. 3



ACT 214472  
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COMBINED DECLARATION AND POWER OF ATTORNEY

Attorney Docket No. AC FZK 4903  
(JT-8)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of subject matter which is claimed and for which a patent is sought on the invention entitled **COMPUTER FOR ANALYZING DATA FROM MEASUREMENTS OF NUCLEAR MAGNETIC RESONANCE, NUCLEAR TOMOGRAPH PROVIDED WITH SAID COMPUTER, AND METHOD FOR ANALYZING DATA FROM MEASUREMENTS OF NUCLEAR MAGNETIC RESONANCE**, the specification is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

199 23 587.2	Germany	May 22, 1999	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)		
_____	_____	_____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number)	(Country)	(Day/Month/Year Filed)		

I hereby claim the benefit under Title 35, United States Code, § 119(e) and/or 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112. I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

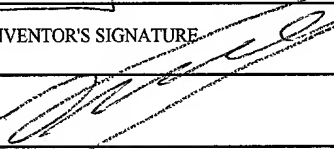
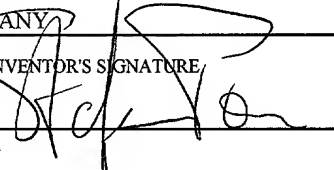
_____	_____	_____
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
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(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
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(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this

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